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Accuracy of multidetector-row CT for restaging after neoadjuvant treatment in patients with oesophageal cancer

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Abstract
Objectives To assess the diagnostic accuracy of 64-multidetector CT (MDCT) for restaging of patients with oesophageal cancer undergoing neoadjuvant therapy.
Methods Results of pathological staging were correlated with those from 64-MDCT before and after neoadjuvant treatment in 35 patients using the American Joint Committee on Cancer/TNM classification (7th edition). CT response was determined using the Response Evaluation Criteria in Solid Tumours (RECIST) method, modified for one-dimensional tumour diameter measurement.
Results 64-MDCT predicted T stage correctly in 34 % (12/35), overstaged in 49 % (17/35) and understaged in 17 % (6/35). Sensitivity/specificity values were as follows: T0, 20 %/92 %; T1–T2, 31 %/59 %; T3, 60 %/64 %; T4, 100 %/4 %. Negative predictive values for T3/T4 were 80 %/100 %. MDCT accurately predicted complete histopathological response in 20 % (accuracy 74 %) and overstaged in 80 %. Tumour regression grade was predicted correctly in only 8 % (2/25) and underestimated in 68 % (17/25). Accurate N stage was noted in 69 % (24/35).
Conclusion Although MDCT tends to be able to exclude advanced tumour stages (T3, T4) with a higher likelihood, the diagnostic accuracy of high resolution MDCT for restaging oesophageal cancer and assessing the response to neoadjuvant therapy has not improved in comparison to older-generation CT. Therefore, the future assessment of oesophageal tumour response should focus on combined morphologic and metabolic imaging.
Key Points
- *Multidetector CT (MDCT) has been beneficial for the evaluation of many tumours.*
- *However diagnostic accuracy for restaging oesophageal cancer has not improved with MDCT.*
- *MDCT tends to be able to exclude advanced tumour stages (T3/T4).*
- *MDCT has a low accuracy for determining lymph node metastasis.*
- *Oesophageal tumour response should be assessed by combined morphological and metabolic imaging.*

Keywords Oesophageal cancer · Multidetector-row computed tomography · Neoadjuvant treatment · Tumour staging · Multislice computed tomography

Abbreviations

AJCC	American Joint Committee on Cancer
CT	computed tomography
CR	histopathological complete response
FDG-PET	fluoro-2-deoxyglucose positron emission tomography
Gy	gray
kVp	peak kilovoltage
mAs	milliampere second
MDCT	multidetector-row computed tomography

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NR	histopathological none response
PET/CT	fluoro-2-deoxyglucose positron emission tomography performed in a hybrid fashion with computed tomography
TRG	tumour regression grade

Introduction

Latest cancer statistics confirm oesophageal cancer to be among the 10 most common malignancies leading to death [1]. The tumours are associated with a high mortality as most tumours are at the time of diagnosis in an advanced stage (T3/T4, N+, or M1) as a result of the late onset of symptoms [1]. So far, surgery remains the main therapy in curable oesophageal carcinoma [2]. By virtue of the poor prognosis of locally advanced oesophageal tumours (T3/T4, N+) with an overall 5-year-survival rate of 42 % after exclusive oesophagectomy, neoadjuvant multimodal treatments are frequently performed before surgery to induce tumour regression and improve outcome [3–7]. Current analysis shows that patients who respond to neoadjuvant treatment have a markedly better prognosis after surgery than non-responders [8, 9]. Meredith et al. [10] showed that patients achieving a histopathological complete response (CR) following neoadjuvant treatment had a 5-year disease free survival and overall survival of 52 % and 52 %, respectively, compared with 22 % and 19 % in non-responders. A disease-specific 5-year-survival rate of even 68 % in complete histological responders after multimodality treatment was shown in a recent multicentre study [11]. The tumour response in patients with squamous cell carcinoma to neoadjuvant therapy may as well identify a group of patients with good prognosis, regardless of whether surgery with a high incidence of postoperative complications will be performed or not [12], and there are intensive discussions globally whether both responders and non-responders should be referred to surgery [13, 14].

Identification of responders and non-responders to preoperative treatment is therefore of paramount importance for prognosis of the individual patient with oesophageal cancer. Imaging plays a crucial role in this task. Endoscopic ultrasound (EUS) has been shown to not accurately predict pathologic stage in patients with oesophageal cancer who have received neoadjuvant treatment. Thus it should no longer be routinely performed for restaging purposes [15, 16]. The most commonly used imaging investigations to reassess patients for resection after neoadjuvant treatment include computed tomography (CT) and positron emission with fluoro-2-deoxyglucose (FDG-PET) preferably performed in a hybrid fashion as PET/CT [2, 13, 14, 17–20]. Several studies have shown that contrast-enhanced CT has limited diagnostic accuracy for evaluation of therapeutic response. Using CT the sensitivity/specificity values for assessment of tumour response of patients with oesophageal cancer undergoing preoperative treatment range between 27–67 % and 33–93 % [21–28]. However, when analysing these studies it has to be pointed out that most were performed with single-slice CT which is no longer state-of-the-art CT equipment. It may been hypothesised that tumour response in patients with oesophageal cancer can be more accurately assessed by MDCT owing to its superior spatial resolution [28].

Therefore, the purpose of our study was to assess the diagnostic accuracy of 64-row MDCT for restaging of patients with oesophageal cancer undergoing neoadjuvant therapy.

Materials and methods

Patients

This retrospective study was approved by our institutional review board, and a waiver of informed consent was obtained. The study was performed in accordance with the principles of the Declaration Helsinki [29]. We retrospectively reviewed charts of 112 patients with biopsy-proven oesophageal cancer who underwent a gastro-oesophageal resection in our hospital between January 2004 and March 2012. Before surgery the clinical tumour stage of any of the included patients was either T3 N0, T1 to T3 with N1 to N3 disease or T4 Nx without metastasis (M0) and the need for neoadjuvant treatment was decided by the institutional multidisciplinary tumour board after careful review of all treatment options for the individual patient. Staging procedures before neoadjuvant treatment included endoscopy with endoscopic ultrasonography with fine-needle aspiration and FDG-PET preferably performed in a hybrid fashion as PET/CT or multidetector CT of the chest and abdomen. A staging laparoscopy for oesophageal tumours of the lower third was optional.

For the current study the patients were only included if a 64-slice contrast-enhanced MDCT of the chest and abdomen before and after neoadjuvant treatment was available for review, whereas the time window between commencement and termination of the neoadjuvant treatment and subsequent surgery should not have exceeded 8 weeks.

Preoperative combined radio-chemotherapy, chemotherapy only, surgery and final patient population

Radio- and chemotherapy were planned in parallel for a duration of 5 weeks. The gross tumour volume included the primary tumour and regional lymph nodes. The clinical target volume included areas at risk for microscopic disease with a 5 cm cranial and caudal margin and a 2 cm lateral

margin. A standard dose of 45–50.4 Gy in 25–28 fractions of 1.8 Gy was applied [30]. Eighteen patients with adenocarcinoma and squamous cell carcinoma were additionally treated with two courses of combination chemotherapy (5-fluorouracil, cisplatin) as described in the literature [31, 32]. Four patients with adenocarcinoma and squamous cell carcinoma intravenously received two cycles of induction therapy with cisplatin and docetaxel. In those patients, chemoradiation started after the second induction chemotherapy cycle. For 5 weeks patients underwent radiotherapy as described above and weekly concomitant intravenous chemotherapy with cisplatin and docetaxel [30].

In 5 patients with adenocarcinoma and squamous cell carcinoma two cycles of induction chemoimmunotherapy with cisplatin, docetaxel and cetuximab were given intravenously. This treatment was followed by chemoimmunoradiation therapy with a radiotherapy standard dose of 45 Gy in 25 fractions of 1.8 Gy and concomitant chemotherapy administered on an outpatient basis with a weekly dose of docetaxel, cisplatin and cetuximab [33].

In 8 patients with adenocarcinoma of the oesophagogastric junction (classified as Siewert I and II) [34], the perioperative treatment consisted of combined chemotherapy with epirubicin, cisplatin and 5-fluorouracil (ECF) only. ECF was administered pre- and postoperatively, three cycles each [35].

Restaging with MDCT was performed 4–5 weeks after completion of neoadjuvant therapy. Surgery was performed 6–8 weeks after completion of the neoadjuvant treatment. Twenty-four patients underwent transthoracic oesophagectomy. In 5 patients transhiatal oesophagectomy was performed. Six patients were treated with total oesophagectomy.

Four patients did not undergo the entire regimen of preoperative therapy and were therefore excluded from the study. A contrast-enhanced 64-slice MDCT before and within 6 weeks after termination of the neoadjuvant treatment was unavailable for review in 73 patients.

The final study population consisted of 35 patients (mean age, 60.4 years; range, 42–73 years) who underwent neoadjuvant treatment with subsequent surgery. This group included 26 men (mean age, 61.1 years; range, 46–70 years) and 9 women (mean age, 58.4 years; range, 42–73 years). The histopathological cell type was adenocarcinoma in 25 patients (71.4 %) and squamous cell carcinoma in 10 patients (28.6 %). In 8 patients the tumour arose from the middle thoracic oesophagus. The lower thoracic oesophagus was involved in 12 patients and the gastro-oesophageal junction in 15 patients. Table 1 displays further specific details of the patient population.

Histopathological analysis and response evaluation

The Mandard grading system was used to determine the histopathological tumour regression in response to neoadjuvant therapy as described in the literature [36]. The grading system is based on the presence of histopathological regressive changes. In grade 1 (complete regression) a specimen showed residual fibrosis without histologically identifiable residual cancer. Grade 2 involved the presence of rare residual cancer cells scattered through the fibrosis. Grade 3 showed an increase in the number of residual cancer cells, but fibrotic tissue still predominated. Grade 4 was characterised by residual cancer outgrowing fibrosis. Grade 5 showed cancer without regressive changes. Tumour regression grade according to Mandard et al. [36] was defined in 26 of the 35 patients in the pathologist's report.

The results of the analysis of the surgical specimen served as standard of reference.

CT protocol

All MDCT examinations of the chest and abdomen before and after initiation of neoadjuvant preoperative treatment were performed using 64-row MDCT (Lightspeed VCT 64; GE Healthcare, Milwaukee, Wis/USA).

Patient preparation included 500 mL of diluted oral contrast medium (Telebrix Gastro; Guerbet AG, Zurich, Switzerland) followed by 30 g barium sulfate oesophageal cream (E-Z-EM, Inc., Lake Success, NY/USA). Eighty to one hundred millilitres of contrast material (Ultravist 300; Bayer Schering Pharma, Berlin, Germany) was administered intravenously by a power injector at a rate of 2 mL/s followed by a bolus of 40 mL saline solution with a 70-s delay (portal venous phase). The thorax and abdomen were examined in the cranio-caudal direction during the portal venous phase (delay, 50–70 s). The following imaging parameters were used: tube voltage, 120 kVp; tube current, 180 mAs with automated modulation technique; section width, 1.25 mm (for a detector configuration 40×1.25 mm); rotation time, 0.6 s; pitch, 1.375. For image reconstruction, a moderately smoothing convolution kernel (B30) and a 512×512 pixel matrix was used. We reconstructed axial images with a section width of 2 mm and an increment of 1.0 mm. Coronal and sagittal reformations were reconstructed using a standard CT workstation with the section width of 2 mm.

Image evaluation

All MDCT data were interpreted in consensus by two experienced radiologists with 15 years and 7 years of experience in interpreting gastrointestinal CT imaging using a picture archiving and communication system workstation (PACS) (Impax 6.4; AGFA Healthcare, Mortsel, Belgium). The two reviewers were blinded to the lesion location, size, clinical and surgical findings as well as the histopathological results. To ensure consistency in the evaluation of the pre- and post-adjuvant

Table 1 Patient characteristics, tumour histology, tumour location, changes in MDCT T and N stage between pre- and post-neoadjuvant therapy and comparison between post-therapy-MDCT and pathological T and N staging; wall thickness changes between pre- and post-therapy MDCT, CT-TRG after neoadjuvant therapy at MDCT and comparison with P-TRG

Patient no./age (years)	G	H	L	T stage			Wall thickness (mm)		Response		N stage		
				Pre-CT	Post-CT	P	Pre-CT	Post-CT	CT-TRG	P-TRG	Pre-CT	Post-CT	P
1/62	M	AC	EJ	T4a	T4a	T3	15	15	SD	/	N2	N2	N3
2/66	M	SCC	Mid	T3	T1/T2	T0	11	7	SD	CR	N0	N0	N0
3/60	M	AC	Low	T4a	T3	T0	24	12	PR	CR	N1	N0	N0
4/65	M	SCC	Mid	T4b	T4b	T0	15	11	SD	CR	N3	N1	N0
5/61	M	AC	Low	T3	T3	T2	19	11	SD	PR	N1	N1	N0
6/42	F	AC	EJ	T3	T3	T2	24	10	PR	DP	N1	N0	N0
7/52	M	SCC	EJ	T1/T2	T3	T0	29	21	SD	/	N1	N0	N0
8/64	M	AC	EJ	T3	T3	T2	27	14	SD	/	N2	N1	N2
9/57	M	AC	EJ	T3	T3	T1	11	11	SD	/	N1	N1	N1
10/73	F	SCC	EJ	T3	T3	T3	14	10	SD	PR	N0	N0	N0
11/47	M	AC	EJ	T3	T3	T3	19	10	SD	PR	N1	N1	N0
12/61	M	AC	Low	T3	T3	T1	13	10	SD	PR	N1	N1	N0
13/63	M	SCC	EJ	T3	T1/T2	T0	10	7	SD	/	N0	N0	N0
14/62	M	AC	Mid	T1/T2	T0	T2	7	3	CR	/	N1	N0	N1
15/54	F	SCC	EJ	T3	T1/T2	T0	15	10	SD	CR	N1	N0	N0
16/50	M	AC	Low	T1/T2	T1/T2	T0	9	8	SD	CR	N0	N0	N0
17/70	M	AC	EJ	T3	T3	T3	20	12	SD	DP	N1	N1	N1
18/58	M	AC	EJ	T3	T3	T3	12	12	SD	SD	N0	N0	N0
19/68	M	AC	Low	T4a	T3	T1	12	12	SD	PR	N2	N0	N0
20/60	M	AC	Low	T3	T1/T2	T0	15	7	PR	CR	N0	N0	N0
21/49	F	AC	Low	T3	T1/T2	T2	15	9	SD	PR	N0	N0	N0
22/52	F	SCC	Mid	T3	T1/T2	T2	12	5	PR	SD	N0	N0	N0
23/61	F	SCC	Low	T1/T2	T0	T0	8	4	CR	/	N0	N0	N0
24/61	F	SCC	Mid	T1/T2	T1/T2	T3	9	6	SD	DP	N0	N0	N0
25/69	M	AC	Low	T4a	T3	T2	17	13	SD	PR	N1	N1	N0
26/68	M	AC	EJ	T3	T0	T0	16	4	CR	/	N2	N0	N0
27/46	M	AC	EJ	T4a	T3	T3	23	23	SD	PR	N2	N0	N1
28/67	M	AC	Low	T3	T3	T3	15	12	SD	SD	N1	N1	N1
29/67	M	AC	Mid	T3	T1/T2	T3	11	6	SD	DP	N2	N1	N3
30/61	F	AC	Mid	T3	T1/T2	T3	10	6	SD	PR	N0	N0	N0
31/63	M	AC	Low	T1/T2	T1/T2	T1	9	8	SD	PR	N0	N0	N0
32/62	M	SCC	Mid	T1/T2	T1/T2	T0	8	6	SD	CR	N1	N1	N1
33/73	F	AC	EJ	T4a	T1/T2	T1	13	8	SD	DP	N2	N0	N0
34/53	M	AC	Low	T0	T0	T1	*	*	*	DP	N0	N3	N1
35/67	M	AC	EJ	T4a	T4a	T4b	22	22	SD	–	N3	N3	N3

MDCT multidetector computed tomography, *CT-TRG* computed tomography tumour regression grade assessed by modified Eastern Cooperative Oncology Group criteria, *P-TRG* pathological tumour regression grade according to Mandard et al. [36], *G* gender, *M* male, *F* female, *H* histology, *AC* adenocarcinoma, *SCC* squamous cell carcinoma, *L* location, *Up* upper thoracic oesophagus, *Mid* middle thoracic oesophagus, *Low* lower thoracic oesophagus, *EJ*, oesophagogastric junction, *Pre-CT* computed tomography before neoadjuvant therapy, *Post-CT* computed tomography after neoadjuvant therapy, *CT-TRG* computed tomography tumour regression grade assessed by modified Eastern Cooperative Oncology Group criteria, *P-TRG* pathological tumour regression grade according to Mandard et al. [36], *P* pathological findings, *CT* computed tomography, * no tumour visible on CT, – no information in pathological report, *CR* complete response, *PR* partial response, *SD* stable disease, *DP* disease progression

therapy studies, data from both examinations were always analysed during the same reading session. Measurements were performed using the electronic calliper of the workstation.

T staging

The tumour was staged by MDCT before and after neoadjuvant therapy according to the 7th edition of the AJCC/TNM classification [37–39]. The deepest tumour invasion determined the main tumour location (cervical oesophagus, upper thoracic oesophagus, middle thoracic oesophagus, lower thoracic oesophagus/ oesophagogastric junction) [39].

To access the tumour depth we defined an oesophageal wall thickness of equal to or wider than 5 mm as pathological [22, 40–42]. Wall thickness was measured perpendicular to the lumen of the oesophagus. If the lumen was not visible the maximal transverse tumour diameter was obtained and multiplied by a factor of 0.5 [24]. The wall thickness was determined at the same tumour level in the preoperative follow-up study as in the baseline examination [28].

By modifying the classification system of Tio et al. [43] and Jones et al. [22] and consistent with the 7th TNM edition [37–39] the according MDCT T status was defined as follows: CT–T0: wall thickness less than 5 mm and without signs of mediastinal involvement. The CT–T1 and CT–T2 stages were combined because it was impossible to differentiate between the oesophageal wall layers on MDCT images. CT–T1 and CT–T2 stages were defined as having a wall thickness of at least 5–10 mm without evidence of mediastinal involvement. CT–T3 stage was defined when the tumour exhibited a wall thickness of greater than 10 mm with mediastinal involvement, but no invasion of adjacent structures was present. A CT–T4a (invasion of pleura, pericardium, diaphragm) and CT–T4b (invasion of other structures e.g. aorta, vertebral body, trachea) were defined if the tumour had a wall thickness of greater than 10 mm and invaded adjacent structures.

N staging

For N staging we included regional lymph nodes extending from cervical perioesophageal to the celiac axis as described in the 7th edition of the AJCC/TNM classification [37–39]. Lymph nodes were regarded to be positive for malignancy with a short axis diameter of at least 10 mm [22, 43–45]. The N status using MDCT was staged as follows: N0 corresponded to no evidence of pathological regional lymph nodes. Metastases in 1–2 regional lymph nodes were staged as N1 and in 3–6 lymph nodes as N2. N3 was defined as metastasis in at least 7 regional lymph nodes [37–39].

M staging

The M staging was described as Mx if distant organ metastasis could not be assessed, M0 if no distant organ metastasis was evident and as M1 if distant organ metastasis was present [37–39].

CT response evaluation

To investigate the tumour response to neoadjuvant therapy at MDCT we used the World Health Organisation (WHO)/Response Evaluation Criteria in Solid Tumours (RECIST) method [46], modified for one-dimensional measurement, and correlated the results with the histopathological tumour regression grade (TRG) as described by Mandard et al. [22, 36]. Absence of tumour on post-treatment MDCT was defined as complete response, correlating with a TRG 1. A decrease of at least 50 % in tumour diameter was described as partial response, correlating with TRG 2. Stable disease matched the criteria of no increase or decrease of less than 50 % or increase of less than 25 % of tumour diameter, corresponding to a TRG 3. An increase of at least 25 % in tumour diameter was defined as a disease progression, being consistent with a TRG of 4 or 5.

Statistics

Statistical analysis was performed by using statistical software (SPSS, version 17.0.1, SPSS, Chicago, Ill; Microsoft Excel 2010). Sensitivity, specificity, positive and negative predictive value as well as accuracy were evaluated. Agreement between histopathology and post-therapeutic T stage, histopathology and post-therapeutic N stage or tumour regression grade, respectively, was determined by calculating Cohen's kappa values for tumour status, nodal status and tumour regression grade. A kappa value of less of 0.4 indicated poor to moderate agreement, between 0.4 and less than 0.75 indicated fair to good agreement and at least 0.75 indicated excellent agreement.

Results

The distribution of T and N stages among the patient population based on MDCT imaging and following histopathological analysis after surgery is displayed in Table 2.

None of the tumours involved the cervical or upper thoracic oesophagus. The primary tumour was visible on MDCT before commencement of the neoadjuvant treatment

Table 2 Histopathological T and N staging characteristics of study population

	T0	T1/T2	T3	T4	Total
N0	10	9	5		24
N1	1	3	3		7
N2		1			1
N3			2	1	3
Total	11	13	10	1	35

T tumour stage, *N* nodal stage

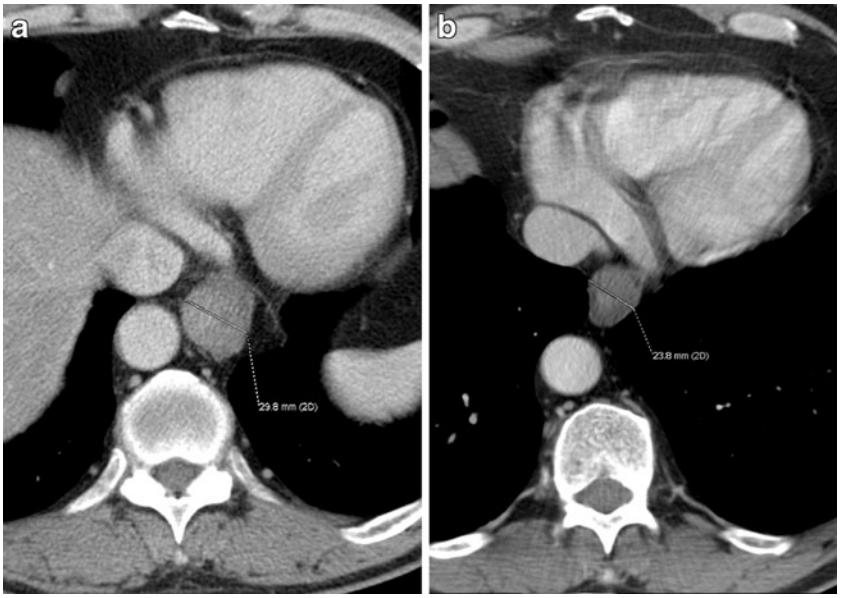

Fig. 1 A 67-year-old, correctly staged patient with adenocarcinoma of the lower thoracic oesophagus histopathological T3 N1 M0 disease. **a** Axial, pre-neoadjuvant therapy, contrast-enhanced MDCT at the level of the coronary sinus shows a circumferential oesophageal wall thickening with obliteration of the lumen. The maximal transverse tumour diameter was obtained and multiplied by a factor of 0.5. **b** Axial, post-neoadjuvant therapy, contrast-enhanced MDCT image obtained at the same level shows a small (<50 %) decrease in oesophageal wall thickness. MDCT correctly predicted tumour regression grade as stable disease and accordingly staged the tumour as T3

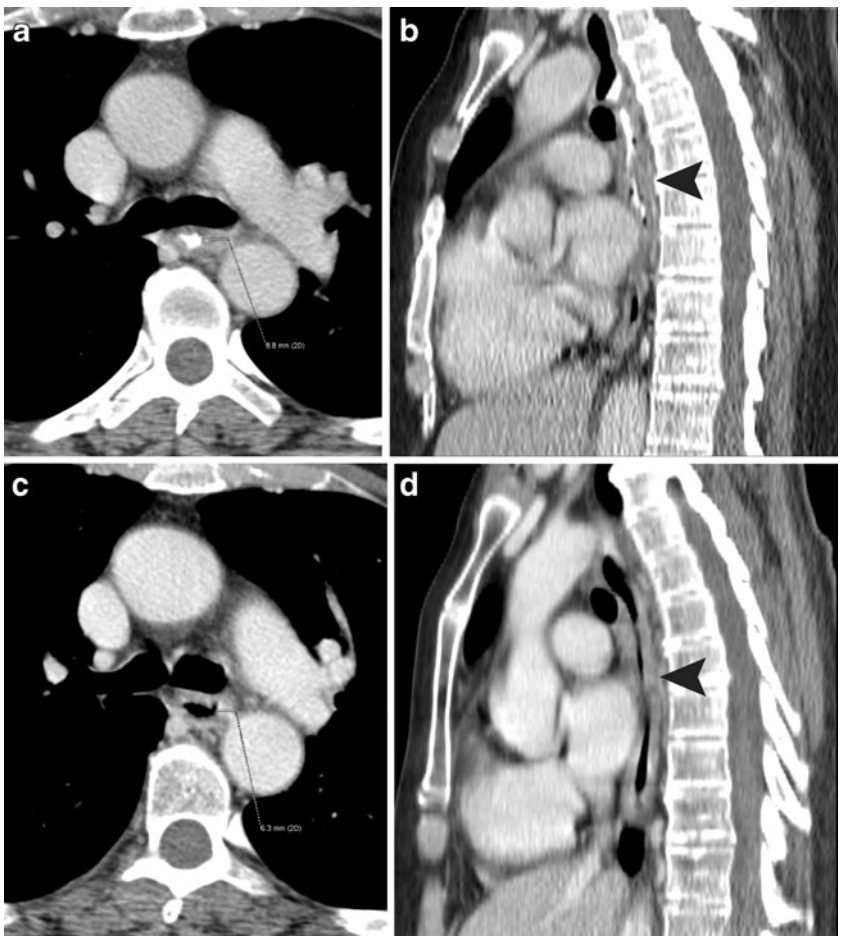

Fig. 2 A 61-year-old, understaged patient with histopathological T3 N0 M0 squamous cell carcinoma. **a** Axial pre-neoadjuvant therapy, contrast-enhanced MDCT shows an oesophageal wall thickening at the level of the left pulmonary artery. **b** Sagittal reformatted MDCT image shows focal dorsal wall thickening of the middle thoracic oesophagus, which was regarded as the location of the primary MDCT T1/2 tumour (*arrowhead*). **c** Axial post-neoadjuvant therapy, contrast-enhanced MDCT obtained at the same level shows a slight decrease in oesophageal wall thickening. **d** Sagittal reformatted MDCT image shows a decrease in focal dorsal wall thickening (*arrowhead*), but the oesophageal wall appears to be generally thickened over a long distance. MDCT misinterpreted the findings as stable disease and understaged the residual tumour as T1/2. Histopathology even showed disease progression and a T3 tumour was found in the surgical specimen

Table 3 Computed data and diagnostic performance of 64-MDCT for T staging

T	*n*	TP	TN	FP	FN	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
T0	11	2	23	2	8	20	92	50	74	71
T1/T2	13	4	13	9	9	31	59	31	59	49
T3	10	6	16	9	4	60	64	40	80	63
T4*	1	1	32	2	0	100	4	33	100	94

MDCT multidetector computed tomography, *T* tumour stage, * T4a and b calculated together, *n* number of patients with histological result, *TP* true positive, *TN* true negative, *FP* false positive, *FN* false negative, *PPV* positive predictive value, *NPV* negative predictive value

in 34/35 (97 %) of cases. The tumour regression grade was evaluated in 25 patients as the tumour was not visible on MDCT in 1 of those 26 patients.

Prediction of post-therapeutic T stage

Overall the T stage was correctly predicted by 64-slice MDCT in 12 of the 35 patients (34 %) (Fig. 1). Overstaging occurred in 49 % (17/35) and understaging occurred in 17 % (6/35) (Fig. 2). Table 3 shows the diagnostic performance of 64-slice MDCT according to tumour stage. The results demonstrated high negative predictive values of 80 % and 100 % for T3 and T4 disease. When comparing the results of the pre- to the post-neoadjuvant therapy MDCT, the patients' T status was downstaged in 46 % (16/35) and upstaged in 3 % (1/35). In one patient the tumour was not visible on MDCT. The kappa value between histopathology and T stage was poor (0.10).

Prediction tumour response

Ten of the 35 patients (28.6 %) showed a complete response (ypT0N0) to neoadjuvant therapy on histopathology. Two of those 10 patients (20 %) showed a complete response on MDCT using our criteria with a sensitivity of 20 %, specificity of 96 %, positive predictive value of 67 %, negative predictive value of 75 % and an accuracy of 74 % (Table 4). 64-slice MDCT overstaged 8 of the 10 complete pathological responders and predicted T1–T2 stage in 5, T3 disease in 2 and T4 stage in 1 patient (Fig. 3). The tumour regression grade was predicted correctly by 64-slice MDCT in a total of only 8 % (2 of 25 patients). The degree of regression was overestimated in 24 % (6/25) and underestimated in 68 % (17/25) of patients. More specific information about the regression grades for the 25 evaluated patients is listed in Table 5. The kappa value between histopathology and tumour regression grade was 0.01.

Prediction of post-therapeutic N stage

MDCT correctly staged the nodal disease in 69 % (24/35), overstaged in 17 % (6/35) and understaged in 14 % (5/35) of patients (Fig. 4). The efficacy of MDCT for the specific N stages is shown in detail in Table 6. Referring to the pre- and post-therapy MDCT the N stage was downstaged in 34 % (12/35) and upstaged in 3 % (1/35). The kappa value between histopathology and post-therapeutic N stage was 0.4

Prediction of M stage

In none of the 35 patients was distant organ metastasis found using MDCT data sets.

Discussion

With only 34 % of patients having the T stage of their disease correctly predicted and 69 % having the N stage accurately predicted, this study demonstrates that restaging of oesophageal cancer after neoadjuvant therapy by high resolution 64-slice MDCT did not improve in comparison to single-slice CT. Therefore, the assumption made by some authors that higher spatial resolution as provided by MDCT technology will improve the diagnostic accuracy of MDCT could not be confirmed [26, 27].

Our results revealed a diagnostic accuracy of 74 % using 64-row MDCT to predict complete pathological tumour response, which is slightly higher as compared with

Table 4 Computed data and diagnostic performance of 64-MDCT for complete histopathological responders (ypT0N0)

	n	TP	TN	FP	FN	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
ypT0N0	10	2	24	1	8	20	96	67	75	74

MDCT multidetector computed tomography, *n* number of patients with histological result, *TP* true positive, *TN* true negative, *FP* false positive, *FN* false negative, *PPV* positive predictive value, *NPV* negative predictive value

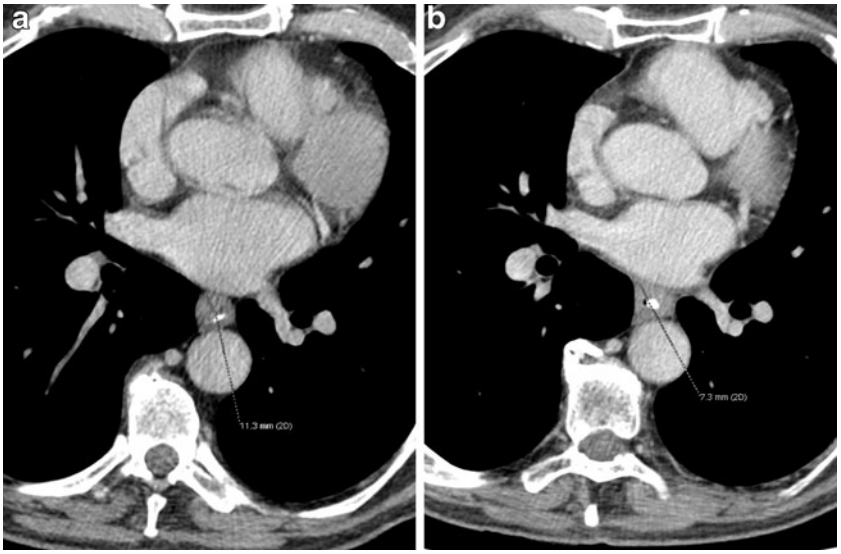

Fig. 3 A 66-year-old, overstaged histopathological complete responder (T0 N0 M0) with squamous cell carcinoma of the middle thoracic oesophagus. **a** Axial pre-neoadjuvant therapy, contrast-enhanced MDCT obtained at the level of the right superior pulmonary vein shows an asymmetric wall thickening of the oesophagus. **b** Decreased thickening of the oesophageal wall on post-neoadjuvant therapy, axial, contrast-enhanced MDCT image obtained at the same level. As a result of the persistent slight wall thickening MDCT predicted stable disease and overstaged the tumour as T1/2 disease. However, the surgical specimen showed complete tumour regression

previous studies. However, the complete responder prevalence of the included patients (only 28.6 %) was lower compared with published studies [22, 24, 25]. Cerfolio et al. [25] showed a prevalence of 31 % complete responders and an accuracy of 71 % for CT to detect complete responders when defining complete CT response as no visible tumour. Jones et al. [22] approached CT response using Eastern Cooperative Oncology Group criteria and dichotomised pathological response (responder versus non-responder) with a prevalence of 42 % responders and an accuracy of 52 %. Other groups [21, 23, 24] used the Mandard et al. criteria [36] to establish pathological response. They differed in the CT approach to determine responders using, for instance, tumour volume reduction of 50 % [21] or WHO criteria [23]. Swisher et al. [24] assessed the maximal oesophageal wall thickness and the relative percent change with treatment, showing that those changes were not significant. Beer et al. [28] showed that early changes in tumour diameter measured at the same level, as is the case in our study, were not significant. However, in the study by Beer et al. [28] only patients with adenocarcinoma restricted to the oesophagogastric junction were investigated using MDCT after 14 days of chemotherapy. We waived 3D-CT tumour volume measurements as van Heijl et al. [47] showed that tumour volume changes after 14 days of neoadjuvant radio-chemotherapy as measured by 3D-MDCT were not associated with histopathological tumour response.

The 74 % accuracy of predicting complete pathological responders and the fact that assessing the pathological tumour regression grade after neoadjuvant therapy with 64-slice MDCT was correct in only 8 % show that post-neoadjuvant therapy 64-slice MDCT cannot differentiate pathological responders from non-responders. Moreover, considering the high rate of overstaged complete pathological responders, we affirm that despite the high resolution of MDCT the differentiation between viable tumour,

Table 5 Computed data and diagnostic performance of 64-MDCT for tumour regression grade

TRG	*n*	TP	TN	FP	FN	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
TRG 1/CR	7	0	18	0	7	0	100	0	72	72
TRG 2/PR	10	0	11	4	10	0	73	0	52	44
TRG 3/SD	3	2	3	19	1	66	14	10	75	20
TRG 4+5/DP	5	0	20	0	5	0	100	0	80	80

MDCT multidetector computed tomography, *TRG* tumour regression grade, *CR* complete response, *PR* partial response, *SD* stable disease, *DP* disease progression, *n* number of patients with histological result, *TP* true positive, *TN* true negative, *FP* false positive, *FN* false negative, *PPV* positive predictive value, *NPV* negative predictive value

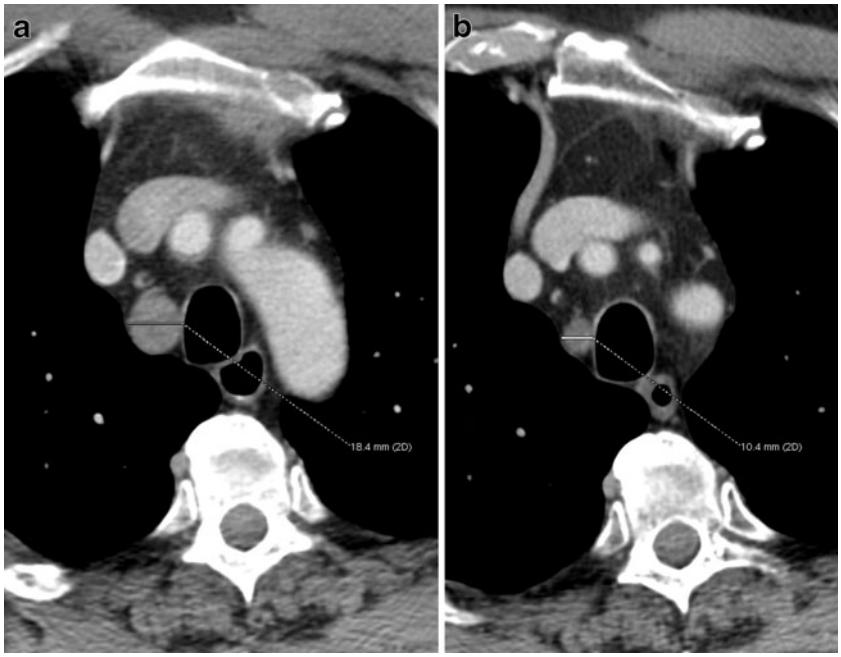

Fig. 4 A 61-year-old patient with histopathological T3 N0 M0 adenocarcinoma of the middle thoracic oesophagus. **a** Axial pre-neoadjuvant therapy, contrast-enhanced MDCT shows an enlarged right paratracheal lymph node above the azygos vein. **b** Post-neoadjuvant therapy, contrast-enhanced MDCT at the same level shows a decreased, now borderline sized 10 mm lymph node. MDCT correctly predicted N0 disease

inflammation and scar tissue after neoadjuvant therapy is not possible using MDCT [26, 41].

Our study confirms the results of previous authors [25, 27, 48] that the ability of MDCT to differentiate between tumours from T1 to T3 stages remains poor as the different wall layers cannot be differentiated (sensitivity 31 %, 60 %; specificity 59 %, 64 % for T1/T2 and T3, respectively). In one patient with pathological T1N1 disease the tumour was not even visible on MDCT.

With regard to the study by Cerfolio et al. [25] which showed an accuracy of 76 % in distinguishing T4 from T1 to T3 disease, our results with high negative predictive values for T3 and T4 disease (80 %/100 %, respectively), although limited by the small number of patients, tend to confirm the trend of MDCT to be able to exclude those advanced tumour stages with a higher likelihood. These findings are important because MDCT is still widely applied for monitoring neoadjuvant therapy, restaging oesophageal cancer and, in consideration of those post-treatment MDCT results, defining the further treatment such as curative surgery or palliative methods.

Regarding the N staging, previous authors described a low diagnostic accuracy of CT for N stage ranging between 52 and 78 %, using cut-off values between 6 and 10 mm for lymph node diameter [21, 22, 25, 49]. Our 64-slice MDCT study also shows a low accuracy of 69 % for determining the N stage, because it is not possible to differentiate between non-enlarged nodal metastasis and normal lymph nodes on MDCT. The result of our study that MDCT is of limited value for restaging of patients with oesophageal cancer following neoadjuvant treatment is in line with the results of the studies which assessed the value of morphologic imaging (including MDCT, MRI and EUS) for restaging of rectal or gastric cancer following neoadjuvant treatment. The reason for the limited value of MDCT in our study might be explained by the fact that changes due to fibrosis, inflammation and residual, viable tumour cannot be reliably distinguished [50, 51] and micrometastasis in normal sized lymph nodes cannot be excluded by morphological imaging [52].

We acknowledge the following limitations. The first and most important limitation is the overall small population with only 10 of 35 patients (28.6 %) being classified as

Table 6 Computed data and diagnostic performance of 64-MDCT for N staging

N	n	TP	TN	FP	FN	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
N0	24	19	9	2	5	79	82	90	64	80
N1	7	4	21	7	3	57	75	36	88	71
N2	1	0	33	1	1	0	97	0	97	94
N3	3	1	32	0	2	33	100	100	94	94

MDCT multidetector computed tomography, *N* nodal stage, *n* number of patients with histological result, *TP* true positive, *TN* true negative, *FP* false positive, *FN* false negative, *PPV* positive predictive value, *NPV* negative predictive value

complete pathological responders (ypT0N0) to neoadjuvant therapy. Owing to the fact that only one patient had histopathological T4 disease, the high sensitivity and negative predictive value have to be interpreted with caution.

Second, considering the likelihood of asymmetric and random tumour regression, we only observed changes in tumour diameter at the same level, ignoring tumour diameter behaviour on upper or lower levels. Despite diameter changes due to post-treatment effects, asymmetric tumour regression could have led to an incorrect designation of tumour behaviour in our study. We waived defining the maximal tumour diameter or tumour volume after therapy, because previous studies showed that those changes on MDCT were not significant [24, 47]. We wanted to analyse the tumour regression by using the modified WHO/RECIST methods [46], because they are a robust, standardised and clinically easily applicable method to access the response to neoadjuvant therapy with 64-slice MDCT for experienced and less experienced radiologists alike.

Third, by only taking the maximal lymph node diameter into consideration we missed the normal sized but pathologically malignant lymph node metastasis. This might have led to an underestimation of nodal disease.

Moreover technical issues regarding the CT protocol such as the lack of a biphasic intravenous contrast agent administration or the use of thinner slices and reconstruction intervals might have influenced the results. Finally, we did not use advanced technical possibilities such as CT perfusion.

We conclude that although MDCT tends to be able to exclude advanced tumour stages (T3, T4) with a higher likelihood, the diagnostic accuracy of high resolution MDCT for restaging oesophageal cancer and assessing the response to neoadjuvant preoperative therapy has not improved in comparison to older-generation CT. Therefore, the future assessment of oesophageal tumour response to neoadjuvant therapy should focus on combined morphologic and metabolic imaging.

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